REMARKS

Claims 1-11 stand rejected. Claim 1 has been amended and support can be found, for example, in the claims and specification as originally filed, and particularly in paragraphs 104-109. Claims 2, 4-10, 14 and 15 have been amended and support can be found in the claims and specification as originally filed. Claims 8-12 have been amended and support can be found, for example, in paragraphs 10-11 and 15. Claims 3, 13, 16, and 17 have been canceled. New claims 18 and 19 have been added and support can be found, for example, in paragraphs 10 and 15.

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Claim objections

Claim 9 stands objected to. It has been amended to correct for informalities and Applicants request the withdrawal of this objection.

Rejection under 35 U.S.C. §112 (second paragraph)

Claims 1-2 and 5-11 stand rejected as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner has asserted that use of the terms "gene" and "encoding", as well as part c) directed to transcription and translational control elements, renders the metes and bounds of claim 1 unclear. Claim 1 has been amended to recite a "second nucleic acid sequence encoding a therapeutic molecule of interest" and "transcription and translational control elements for directing expression" [Emphasis added]. As such, it would be clear to a person of ordinary skill in the art that the term "molecule" is encoded by the second nucleic acid and that separate control elements are provided for the first and the second nucleic acid sequences. Claim 6 has been amended to remove the phrase "the intracellular domain" in the claim. Applicants respectfully submit that the claims are clear and definite and request the withdrawal of these rejections.

Rejection under 35 U.S.C. §101

The Examiner has asserted that the claimed invention is directed to non-statutory subject matter because the claims read on the full-length CD8 α-chain encoded by the wild-type animal. As currently amended, claim 1 and all claims depending therefrom require an "isolated polypeptide." As such, Applicants respectfully submit that the claimed invention is directed to statutory subject matters and request the withdrawal of this rejection.

Rejections under 35 U.S.C. §102

Claims 1-2 and 5-6 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by U.S. Patent No. 5,540,926 to Aruffo et al. (hereinafter "Aruffo"), as further evidenced by WO 04/042346 to Wohlgemuth, et al. and SEQUENCE COMPARISON 1 OF 9/6/06. Claims 1, 3-6, 8-9, and 10 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Bonyhadi, et al. (1997) J. Virol., 71(6): 4707-16 (hereinafter "Bonyhadi"). Applicants respectfully disagree. For an anticipation rejection under 35 U.S.C. §102 to be proper, a single reference must expressly or inherently disclose each and every element of a claim. In re Paulsen, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994); MPEP § 2131 (citing Richardson v. Suzuki Motor Co., 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

1. The present invention is not anticipated by Aruffo.

As currently amended, claim 1 recites first and second nucleic acid sequences, with separate transcription and translational control elements for directing expression of each sequence. The Examiner asserts that "Aruffo discloses the preparation of soluble GP39 ... linked to human CD8, which minimally comprises its extracellular domain (e.g., col. 8, paragraph 5)." (Page 6, 2nd paragraph of the Office Action). The portion of Aruffo cited by the Examiner discloses CD8 as a suitable "tag protein", which is indicative of a soluble GP39-CD8 fusion protein, the expression of which is presumably driven by a single set of control elements. However, the present invention is directed to a polynucleotide including a "first nucleic acid sequence encoding a CD8 α-chain ...; a second nucleic acid sequence encoding a therapeutic molecule of interest; and ... transcription and translational control elements for directing

expression of said first and said second nucleic acid sequences." This is not a fusion protein construct. As such, Aruffo fails to disclose each and every element of the present invention Applicants respectfully submit that the claimed invention is not anticipated by Aruffo and request the withdrawal of this rejection.

1. The present invention is not anticipated by Bonyhadi.

As currently amended, claim 1 recites "a CD8 α-chain polypeptide comprising a CD8 α-chain extracellular domain". In contrast, Bonyhadi discloses "a modified MMLV vector, LmiLy, which encodes the transmembrane and cytoplasmic portions of the cell surface marker Lyt2 (the murine homolog of human CD8α)" [Emphasis added]. In addition, currently amended claim 1 recites first and second nucleic acid sequences with transcription control elements and translational control elements for directing expression of each sequence. Bonyhadi discloses a construct having a single transcription promoter region (LTR), which yields a single transcript (See legend of Fig. 1A) for both REVM10 and Lyt 2.

As such, Bonyhadi fails to disclose each and every element of the present invention. Applicants respectfully submit that the claimed invention is not anticipated by Bonyhadi and request the withdrawal of this rejection.

Rejection under 35 U.S.C. §103

Claims 1-2, 5-6, and 8-10 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Aruffo and U.S. Patent No. 6,193,980 to Efstathiou, et al. (hereinafter "Efstathiou"), as further evidenced by WO 04/042346 to Wohlgemuth, et al. and SEQUENCE COMPARISON 1 OF 9/6/06. Claims 1-2, 5-6, and 8-9 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Aruffo and U.S. Patent No. 6,509,150 to Salvetti, et al. (hereinafter "Salvetti"), as further evidenced by WO 04/042346 to Wohlgemuth, et al. and SEQUENCE COMPARISON 1 OF 9/6/06. Claims 1-2, 5-6, 8, and 11 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Aruffo and U.S. Patent No. 6,207,456 to Baru, et al. (hereinafter "Baru"), as further evidenced by WO 04/042346 to Wohlgemuth, et al. and SEQUENCE COMPARISON 1 OF 9/6/06. Claims 1, 3-7, and 5-9 stand rejected under 35

U.S.C. §103(a) as allegedly being unpatentable over Zimmer, et al. (1990) Molecular Medicine 5(4): 244-53 and Bonyhadi. Claim 10 stands rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Zimmer and Bonyhadi, as applied to claims 1, 3-7, and 5-9 above, and further in view of Liang, et al. (2002) Gene Therapy, 9:1659-66 (hereinafter "Liang")

Applicants respectfully disagree. A *prima facie* case of obviousness requires that there be some suggestion or motivation in the reference or in the knowledge generally available to one of ordinary skill in the art to modify the reference, which must be found in the prior art and not based on applicants' disclosure. *See In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

1. The claims are non-obvious over Aruffo and Efstathiou, Salvetti, or Baru .

The present claims recite a polynucleotide including a "first nucleic acid sequence encoding a CD8 α-chain polypeptide; [and] a second nucleic acid sequence encoding a therapeutic molecule of interest", the expression of which is directed by separate transcription and translational control elements for the first and the second sequences. As discussed above and as the Examiner has correctly recognized in his remarks, the present invention does not concern fusion proteins having a CD8 polypeptide portion, such as those disclosed by Aruffo. This reference requires a CD8 fusion protein as indicated by its disclosure that the

> fusion proteins of the invention may further comprise a molecular "tag", ... which replaces the transmembrane and cytoplasmic domains of gp39 and provides a "handle" that reacts with reagents. [Col. 8, lines 11-15]

The recovery of fusion proteins in Aruffo is through binding of the CD8 "tag" (See Col. 14 line 67 through Col. 15 line 4). As such, there is no motivation or suggestion to a person of ordinary skill in the art to modify the construct of Aruffo to express "a CD8 α-chain polypeptide" and "a therapeutic molecule of interest" as anything other than a fusion protein.

In addition, as the Examiner is aware, a "prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983)." M.P.E.P. §2141.02 VI. Aruffo teaches away from the present invention. As previously discussed, the reference requires a CD8 polypeptide portion to be fused to the portion of gp39 protein, as expressly recited in claims 4 and 13. Any modification of Aruffo towards a non-CD8

polypeptide fusion protein would lead away from the invention contemplated by the reference. Therefore, as a whole Aruffo teaches away from the present invention. The Applicants respectfully submit that a *prima facie* case of obviousness has not been established.

2. The claims are non-obvious over Zimmer and Bonyhadi.

Zimmer discloses an "E1-deleted recombinant adenovirus containing ... mouse ... or human OTC cDNA ... driven by a CMV promoter" (p. 245 2nd column under Animals and Adenoviral Vectors). The Examiner asserts that

> it would have been obvious to modify the methods of Zimmer with those of Bonyhadi, to arrive at an adenoviral vector comprising transgenes for CD8-alpha, lacking its cytoplasmic tail, and for ornithine carbamoyl transferase.
> [Page 11 of the Office Action]

The Applicants respectfully disagree. As previously discussed, claim 1 as presently amended requires a "CD8 α-chain extracellular domain." Bonyhadi discloses a murine CD8 α-chain that includes only the transmembrane and cytoplasmic portions. As such, there is no motivation in the reference to modify Zimmer to reach the present invention.

Also, currently amended claim 1 recites first and second nucleic acid sequences, with transcription control elements and translational control elements for directing expression of each sequence. As previously discussed, Bonyhadi discloses a construct with a single promoter region that yields a single transcript. The transcript contains an internal ribosome entry site (IRES) located between the REVM10 and Lyt2 nucleic acid sequences, which allows for the initiation of translation in the middle of a single mRNA transcript. As such, Bonyhadi only motivates a person of ordinary skill in the art to modify Zimmer's adenoviral vector to include a single CMV promoter, an OTC nucleic acid sequence, a Lyt2 nucleic acid sequence, and an IRES sequence positioned in between the OTC and Lyt2 sequences. Transcription from such a vector would be driven by a single promoter resulting in a single transcript. In contrast, the present invention is directed to a polynucleotide having a "first nucleic acid sequence encoding a CD8 α-chain polypeptide; [and] a second nucleic acid sequence encoding a therapeutic molecule of interest", the expression of which is directed by transcription and translational control elements for the first and for the second sequences. As such, there is no motivation or

suggestion to a person of ordinary skill in the art to modify the vector of Zimmer to reach the present invention. The Applicants respectfully submit that a *prima facie* case of obviousness has not been established.

3. The claims are non-obvious over Zimmer, Bonyhadi and Liang.

As previously discussed, the currently amended claims include a "CD8 α-chain extracellular domain" requirement. Zimmer and Bonyhadi exclude the extracellular domain of the CD8 α-chain. Liang does not concern the CD8 α-chain. The claims also recite a polynucleotide requiring separate transcription and translational control elements for a first and a second nucleic sequences. As previously discussed, Zimmer and Bonyhadi only motivate a person of ordinary skill to reach a vector having a single promoter that yields a single mRNA transcript. Liang does not relate to separate transcription and translational control elements for a first and a second nucleic acid sequence. As such, a person of ordinary skill in the art would not be motivated to modify Zimmer in view of Bonyhadi and Liang to reach the present invention. The Applicants respectfully submit that a *prima facie* case of obviousness has not been established.

Prompt and favorable consideration of this Response is respectfully requested. Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Respectfully submitted,
DORSEY & WHITNEY LLP

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By: J. P. Bernhardt

Jeffery P. Bernhardt, Reg. No. 54,997 for
Todd A. Lorenz, Reg. No. 39,754

Customer Number: 32940
Dorsey & Whitney LLP
Intellectual Property Department
555 California Street, Suite 1000
San Francisco, CA 94104-1513
Telephone: (415) 781-1989
Facsimile: (415) 398-3249